Volume 20, Number 5

Shands at the University of Florida

May 2006

Drugs & Therapy

B • U • L • L • E • T • I • N

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met April 18, 2006. 2 drugs were added in the *Formulary* and no drugs were deleted. 1 drug was reviewed, and a procedure was established to allow patients to use their own supply while they are inpatients.

◆ ADDED

Anastrozole
(Arimidex® by AstraZeneca Pharmaceuticals)

Nelarabine
(Arranon® by GlaxoSmithKline)*

**Restricted to credentialed chemotherapy prescribers*

◆ DELETED

None

◆ EVALUATED BUT NOT ADDED

Isotretinoin
(Accutane® & generics)†

†*High-priority nonformulary drug. Patients must use their own supply.*

Anastrozole was evaluated for addition in the *Formulary* because of high volume nonformulary use. Anastrozole is a common chronic home medication that is continued in women with breast cancer when they are admitted to Shands. In 2004, anastrozole was in the top 200 drugs based on sales (ie, 161) in the US. Other similar aromatase inhibitors used in the treatment of breast cancer (eg, letrozole and exemestane) are not used as commonly, nor are they frequently requested via the nonformulary process. The guidelines for breast cancer published by the National Comprehensive Cancer Network (NCCN) state that the 3 third-generation aromatase inhibitors have similar antitumor efficacy [in breast cancer] and toxicity profiles.

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PEDIATRICS

Pediatric drug research still needs improvement

Healthcare professionals working with pediatric patients understand how difficult it is to find drug information. Frequently drugs are developed and tested only in adults, requiring prescribers to guess appropriate pediatric doses, which can lead to unnecessary adverse events. In 1994 a study found that 6 of the 10 most commonly prescribed drugs for children had no pediatric labeling.[1]

The need for more pediatric data was recognized in 1997 when the Food and Drug Administration Modernization Act of 1997 (FDAMA) was established. As an incentive for conducting pediatric research, manufacturers were given a 6-month extension of the patent on a specific drug if they agreed to do pediatric testing on that drug. The goal of this provision was to improve the understanding of the effects of existing drugs on the pediatric population.

It is well known that we need more research in the pediatric population. Offering an incentive to manufacturers was a good idea and has provided us with some additional pediatric drug information.

There was, however, a major problem with this Act. There was no deadline as to when a pharmaceutical company had to submit their findings and add them to drug labels. Therefore, several drugs went more than a year without label changes once the sponsor was granted patent extension. The FDA reported having difficulty convincing drug manufacturers to list unfavorable pediatric research results on their labels. For example, only 2 out of 8 companies initially reported the negative results of the pediatric research in the use of antidepressants in major depression.

When the Food and Drug Administration Modernization Act expired in January 2002, Congress passed the Best Pharmaceuticals for Children Act (BPCA). Under this Act, the FDA and all application holders have 180 days to negotiate the labeling changes. At the end of this period, the FDA will publish the requested labeling change, along with a copy of the clinical report. If no agreement is reached, the FDA will state the recommendation to the Pediatric Advisory Subcommittee for review. This committee has up to 90 days to review the recommendation and make a decision about label changes. The application holder then has 30 days to comply with the labeling changes.

In the previous Act, studies were not done if a manufacturer opted not to conduct pediatric trials. There was little incentive for a patent extension for a drug that did not generate large revenues. Under the BPCA, however, funds are allotted to allow the FDA to contract for the testing of the drugs when a manufacturer does not want to perform pediatric studies. Therefore, taxpayers are funding drug studies that manufacturers do not conduct, which averages about $3.78 million per drug.[2]

Additionally, this Act provides a process for studying off-patent drugs. The National Institutes of Health (NIH) and FDA develop an annual list of drugs

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Formulary update, *from page 1*

Anastrozole is a nonsteroidal inhibitor of aromatase that prevents the conversion of androgens to estrogens in peripheral tissues. It is used as adjuvant hormonal treatment in postmenopausal women with breast cancer. By suppression of estrogen production, development of estrogen-dependent breast cancer tumors is inhibited.

After local treatment of breast cancers, anastrozole is given to prevent or delay the subsequent appearance of clinically occult micrometastatic disease. These micrometastases are thought to account for distant treatment failures among women undergoing local treatment alone (ie, surgery with or without radiation therapy).

Anastrozole has a labeled indication for adjuvant treatment of postmenopausal women with hormone-receptor-positive early breast cancer. It also has labeled indications as first-line treatments of postmenopausal women with hormone-receptor-positive or hormone-receptor-unknown locally advanced or metastatic breast cancer and for use in the treatment of advanced breast cancer in postmenopausal women with disease progression following tamoxifen therapy.

There are several trials published demonstrating the effectiveness of anastrozole in the treatment of breast cancer in postmenopausal women. The Arimidex, Tamoxifen Alone or Combination (ATAC) trial in postmenopausal women with early breast cancer showed longer disease-free survival and longer time to recurrence than in the tamoxifen group. Distant metastases and contralateral breast cancers were also less in the anastrozole group. There were fewer withdrawals due to adverse effects in the anastrozole group and fewer serious adverse events. Patients treated with anastrozole had less endometrial cancer, thromboembolic events, ischemic cerebrovascular events, vaginal bleeding, hot flushes, and vaginal discharge. Tamoxifen had fewer fractures and less arthralgia.

NCCN guidelines for breast cancer recommend anastrozole as first-line hormonal adjuvant therapy in postmenopausal women either initially or after 2-3 years of tamoxifen. Tamoxifen is now used in patients intolerant of aromatase inhibitors or for whom there is a contraindication to an aromatase inhibitor.

Nelarabine was evaluated as part of the comprehensive review of oncology drugs listed in the *Formulary.* Injectable drugs with potential uses in the inpatient setting that are not listed in the *Formulary* can be problematic to obtain. Nelarabine was approved for use near the end of 2005. It is used for rare forms of cancer, and inpatient use is anticipated to be infrequent.

Nelarabine is a purine analog with labeled indications for the treatment of T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) in pediatric and adult patients whose diseases have not responded to or have relapsed following treatment with at least 2 chemotherapy regimens. Nelarabine is the only drug with labeled indications for these types of cancer.

Nelarabine is considered an orphan drug because its labeled indications are rare. T-ALL is diagnosed in only about 700 patients per year in the US, while T-LBL is diagnosed in only about 900 patients per year.

Nelarabine is a water-soluble purine analogue cytotoxic agent and stops DNA synthesis, which results in cell death. Nelarabine is relatively selective for T-lymphocytes by increasing deoxyguanosine triphosphate (dGTP).

Nelarabine has been evaluated in two phase 2 studies with refractory or recurrent T-cell malignancies (T-ALL or T-LBL). Nelarabine showed partial and complete response improvements in both studies. Although these improvements were modest, the demonstrated effectiveness in refractory disease led to its approval by FDA's accelerated drug approval process. Additional studies will be required to better define nelarabine's safety and efficacy.

Nelarabine has a black-box warning regarding the potential for serious neurological events. Neurological toxicity is the dose-limiting toxicity and is manifested as both central and peripheral effects. Close monitoring for neurological events is strongly recommended.

The dosage recommended is 1500 mg/m2 on days 1, 3, 5 of a 21-day cycle in adults. The recommended dosage is 650 mg/m2 for 5 consecutive days of a 21-day cycle in pediatric patients. The duration of therapy is not established.

Treatment in an adult costs about $12000 for each cycle in adults and $4000 in children. It is anticipated

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Pediatrics, *from page 1*

that are off patent and off exclusivity. The list may also include certain on-patent drugs, which are not voluntarily studied by pharmaceutical manufacturers. Bumetanide, rifampin, lithium, and spironolactone are a few of the off-patent medications that have been on this list. The FDA promotes the study of these drugs, either by the drug's application holders or by third parties (universities, teaching hospitals, laboratories, and pediatric pharmacology research units).

When pediatric studies were conducted under the previous Act, the data was not easily accessible. The Best Pharmaceutics for Children Act, however, states that a summary of the medical and clinical pharmacology reviews of pediatric studies conducted must be made available to the public. The "pediatric studies review summaries" can be accessed from the Food and Drug Administration (FDA) Web site. Currently there are 60 medical and clinical pharmacology reviews available.

Although the BPCA promotes more studies in children, its incentive structure forces consumers and taxpayers to cover the costs of testing. According to an FDA estimate in 2001, pediatric exclusivity raises the cost of prescription drugs by $695 million a year and costs generic drug companies and pharmacies $884 million a year in lost sales. It was reported that AstraZeneca grossed $1.4 billion for Prilosec® and Eli Lilly $900 million for Prozac® during their 6-month patent extensions.[3] Many pediatric drug studies could be funded with this amount of money.

Congress is, however, trying to find a way to reduce the financial burden on consumers. Recently a senator proposed the Lower Priced Drugs Act that would limit the current extension to drug products that are newly labeled with information about the use of drugs in children, apply the extension only to drugs in the dosage form that was tested in children, and put a 3-month cap on the patent extension. In addition to the financial burden on consumers, there are other problems that exist with the current incentive. Should we have to wait until the end of a drug's patent life to get pediatric information? Since patents last 20 years, it would seem reasonable to find a way to make the incentive greater if the research is done earlier in the patent life.

It is well known that we need more research in the pediatric population. Offering an incentive to manufacturers was a good idea and has provided us with some additional pediatric drug information. The 6-month patent extension has, however, cost consumers millions of dollars and has not been as productive as hoped. Additional support could help fill the void of evidence-based information about drug use in children.

By Shannon Williams, PharmD

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1. Food and Drug Administration: The Pediatric Exclusivity Provision: January 2001 Status Report to Congress.
2. Public Citizen Congress Watch, Patently Offensive: Congress Set to Extend Monopoly Patents for Cipro and other Drugs, http://www.citizen.org/documents/ACF34F.PDF).
3. H.R. Rep No. 107-227, at 56 (2001)

Formulary update, *from page 2*
that most nelarabine treatments will be given in the outpatient setting and that only a few patients will receive inpatient treatment with nelarabine.

Isotretinoin (also known as 13-cis retinoic acid) is an oral retinoid with a labeled indication for severe recalcitrant cystic acne. It has also been used off-label for a variety of oncology uses including: cervical cancer, head and neck cancer, squamous cell cancer of the skin, juvenile chronic myelogenous leukemia (CML), and neuroblastoma.

The formulary status of isotretinoin was re-evaluated when it was requested for nonformulary use in a child for whom the drug was required as part of her chemotherapy protocol. The protocol did not provide investigational isotretinoin, and changes in the isotretinoin limited distribution program delayed treatment.

Because of its potential to cause severe teratogenic effects, isotretinoin is only available via a limited distribution program called the iPLEDGE Program (ie, https://www.ipledgeprogram.com/). This program has strengthened requirements compared to the previous Accutane® limited-distribution program. Since isotretinoin is now available from generic manufacturers, the current limited-distribution program is a computer-based program coordinating access from all manufacturers. The goal is to prevent women from becoming pregnant while taking isotretinoin.

Female patients of childbearing potential must select and commit to use 2 forms of effective contraception simultaneously for 1 month before, during, and for 1 month after isotretinoin therapy. She must have 2 negative urine or blood (serum) pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial isotretinoin prescription. The first pregnancy test is a screening test and can be conducted in the prescriber's office. The second pregnancy test must be done in a CLIA-certified laboratory according to the package insert. With each month of therapy, the patient must have a negative result from a urine or blood (serum) pregnancy test conducted by a CLIA-certified laboratory before receiving each prescription.

Each month, the prescriber must enter the female patient's pregnancy results and the 2 forms of contraception she has been using in the iPLEDGE system. The iPLEDGE system verifies that the prescriber, patient, and pharmacy have met all criteria before granting the pharmacy authorization to fill and dispense isotretinoin. The pharmacist must obtain authorization from the iPLEDGE system via the program's Web site or phone system before dispensing each isotretinoin prescription for both male and female patients.

Although a hospital pharmacy can be a registered pharmacy in the iPLEDGE system, the system was designed for the community pharmacy setting. For example, a 30-day supply must be dispensed at a time (ie, no unit dose packaging of a day's supply could be dispensed).

The Shands Medical Plaza (SMP) Pharmacy is already registered in the iPLEDGE system, and there is a designated "responsible pharmacist." The SMP Pharmacy has agreed to fill prescriptions for registered inpatients and prescribers so that isotretinoin can be used as a "Patient's Own Medication" when isotretinoin is needed for inpatient use.

Isotretinoin has been categorized as a "high-priority" nonformulary drug, which requires pharmacists to immediately contact the prescriber to facilitate the use of the patient's own supply of medication.

Since some of the off-labeled oncology uses are in children who are not capable of becoming pregnant, the requirements may seem unreasonable. However, the program is designed for the FDA-labeled indications, not off-labeled uses.

DRUG INFORMATION FORUM

Can generic levothyroxine be used for brands?

Levothyroxine is used for thyroid hormone replacement therapy in patients that are hypothyroid. Since this is a relatively common condition and patients generally take therapy for their entire lifetime, it is no surprise that levothyroxine is taken by many patients seen by physicians.

The Synthroid® brand of levothyroxine was the 4th most commonly prescribed brand name drug in 2005, while Levoxyl® was 24th and Levothroid® was 96th, respectively.[1] Generic levothyroxine was the 9th most commonly prescribed generic drug in 2005.[2] Compared with the previous year, the use of brand name levothyroxine in the community setting is decreasing (ie, between 18-35% depending on the brand) while the use of generic levothyroxine is increasing (ie, 185%).

Levothyroxine has been on the US market for more than 50 years. It is amazing that brand name products are still so common for a drug that has been around for more than a half century. Levothyroxine was marketed before 1962 when new federal laws began to require that new drugs be proven safe and effective. Drugs on the market before 1962 did not have new drug applications (NDAs). Often there are limited bioequivalency data on drugs that do not have NDAs. Drugs without NDAs are not listed in the FDA's list of products that have been tested and shown to be equivalent (ie, *The Orange Book*).

In 1997, the FDA required levothyroxine manufacturers to submit NDAs for their products in order to stay on the market. This action was taken because of reports of inconsistent effects of the marketed products. There are now 9 different levothyroxine products approved by the FDA (ie, products with NDAs), although not all of these products may be marketed.

Whether levothyroxine products can be generically interchanged is a common question received by the Drug Information Service. In the State of Florida, this question is easy to answer; none of the brand-named versions of levothyroxine can be interchanged in the outpatient setting. The State of Florida has a Negative Formulary that prohibits generic interchange for a small number of products. This short list includes levothyroxine.

However, the Negative Formulary does not apply to the inpatient setting where generic interchange of levothyroxine products is common. P&T Committees can approve generic interchange if there is sufficient scientific evidence to justify the practice.

Whether levothyroxine can be interchanged in the community setting in other states is not as easy to answer. As manufacturers have begun testing the bioavailability of their products against each other, confusion about which products are "equivalent" to each other has occurred. *The Medical Letter* concluded that there is no evidence that any particular brand name product is superior to a generic formulation.[3]

Since Synthroid® is the market leader, it is the product that is most often a candidate for generic interchange. There are 5 products that are rated in *The Orange Book* as being bioequivalent to Synthroid®: Levoxyl®, Unithroid®, Levo-T®, and generic products made by Mylan and Genpharm. Levoxyl®, the second most commonly dispensed levothyroxine brand, has 4 products that have been rated as generically equivalent: Synthroid®, Unithroid®, Levo-T®, and Mylan's generic product. The Gen-

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Drugs & Therapy
B · U · L · L · E · T · I · N

Volume 20, No. 5 May 2006
This publication is produced by the Drug Information and Pharmacy Resource Center under the direction of the Department of Pharmacy Services and the Pharmacy and Therapeutics Committee.

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pharm generic has not been shown to be bioequivalent to Levoxyl®. There are no generic equivalents for Levothroid®.

To make matters even more complicated, there are 2 approved levothyroxine products that have not been proven equivalent to any other product: Novothyrox® (by Genpharm) and Levolet®. Generic levothyroxine by Genpharm is interchangeable for Synthroid® but Novothyrox® is not.

Adding to this confusion, the American Thyroid Association, Endocrine Society, and American Association of Clinical Endocrinologists oppose the interchange of brands of levothyroxine—even those deemed interchangeable by the FDA. Regardless of the brand (or generic), these organizations recommend additional monitoring when a patient is switched to a different manufacturer's product. A recently published treatment guideline by *The Medical Letter* recommends, "It is generally advisable to use the same levothyroxine product (a single brand or generic) for any given patient throughout treatment…[and that] Thyroid function tests be checked 6 weeks after any change in levothyroxine formulation."[4]

FDA disagrees with these recommendations. FDA feels additional monitoring is not needed when products have been shown to be bioequivalent by their standards in healthy volunteers. If this monitoring is done (ie, TSH levels), it adds to the overall cost of care. FDA argues that there is no scientific evidence to show negative outcomes with the use of generic levothyroxine. Further, they argue that other narrow therapeutic index drugs (eg, warfarin, digoxin, and phenytoin) are routinely interchanged without incident.

All inpatients at Shands at UF receive Synthroid® brand of levothyroxine. This decision was made because Synthroid® is the only brand of levothyroxine that is available in unit-dose packaging, and Synthroid® is competitively priced with generics in the inpatient setting. If a patient admitted receiving another brand (or generic version) of levothyroxine, they will be treated with Synthroid® during their hospitalization unless they use their own supply of medication.

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1. Anon. Top 200 brand-name drugs by units in 2005. Drug Topics March 20, 2006, pg 25.
2. Anon. Top 200 generic drugs by units in 2005. Drug Topics March 20, 2006, pg 26.
3. Anon. Generic levothyroxine. Med Lett Drug Ther 2004; 46.77.
4. Anon. Drugs for hypothyroidism and hyperthyroidism. Treatment Guidelines 2006;4:17-24.

To Report an Adverse Drug Reaction

Call the ADR Hotline: 5-ADRS (5-2377)

PROVIDE:

- Patient's name
- Patient's location
- Suspected drug(s)
- Type of reaction
- Whether the reaction was — probable, possible, or definite
- Your name and pager # or extension

And we'll do the rest!

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☎ ADR HOTLINE: 5-ADRS